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Does Low Frequency Neuromuscular Stimulation modulate Ergoreflex Activity in Advanced Heart Failure?

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ABSTRACT

Background: Heart failure is a syndrome characterized by cardiac dysfunction, myocardial impairment or loss, with either left ventricular dilation or hypertrophy or both, responsible for it's cardinal manifestations of dyspnea, fatigue and exercise intolerance. Purpose: To determine the effect of low frequency neuromuscular stimulation on ergoreflex activity in advanced heart failure. Methods: Thirty patients of both sexes (7 women and 23 men) with advanced heart failure were included in this study with mean age of 60.13 years. They were chosen from outpatient clinic, Eldemerdash university hospital. They were assigned in a single group which received eight weeks (four times a week) of increasing amplitude low frequency neuromuscular stimulation on Quadriceps and calf muscles after thorough assessment of ergoreflex, ejection fraction and assessment of disability via Minnesota Living with Heart Failure Questionnaire. Results: Statistical significant alteration of ergoreflex contribution associated with decreased disability without any statistically significant changes in ejection fraction. The percentages of changes in minute ventilation (VE) and carbon dioxide dioxide production (VCO2) and maximum oxygen production (VO2) were 37.83%, -36.38% and 25.46% respectively. These changes were associated with improved functional, emotional and psychological status of the patients with a decline of Minnesota Living with Heart Failure Questionnaire score by -29.87% without any significant statistical change in ejection fraction with a change percentage of 2.06%.Conclusion: eight weeks of low frequency neuromuscular stimulation altered ergoreflex contribution leading to a higher functional levels without causing significant central changes regarding ejection fraction. *Key Words: Heart Failure/Low Frequency Neuromuscular Stimulation/ Muscles/ Ergoreflex.*

INTRODUCTION

Patients with Heart failure (HF) suffer from limitations regarding their physical activity pronounced with higher degrees of ventilation compared with normal individuals [1]. A hypothesis has developed, which explains this abnormal response to an exaggerated reflex known as ergoreflex developing with peripheral muscle abnormalities in chronic heart failure. The skeletal muscle, when it becomes abnormal in heart failure (HF), would show changed patterns of the cardiorespiratory control, manifested in symptoms such as dyspnea, fatigue and increased ventilation, usually reported by HF patients [2].

According to such hypothesis, it would be more suitable and effective to treat the cause, the musculoskeletal abnormalities, instead of managing the results of ergoreflex activation, such as peripheral vasoconstriction and sympathetic activation. Randomized and controlled studies have shown that physical training increases oxygen consumption and improves the neurohormonal balance in heart failure (HF) [1].

Physical training, which would affect the muscle tremendously, can be an integral part of the therapy in these patients. However, these interventions are usually only appropriate in patients with moderate symptoms. Patients with more advanced CHF are often excluded due to excessive symptoms and dyspnea[3]. Therefore other interventions are recommended to cause muscle alteration without cardiac strain, in fact, Electrical Muscle Stimulation (EMS), in particular Low Frequency Neuromuscular stimulation (LF-NMES), has been proposed as an interesting alternative to interval training, since it is simple, well-tolerated by patients with CHF, and produces an intense exercise stimulus to the peripheral muscles with low cardiac

MATERIAL AND METHODS

Participants

Thirty patients of both sexes (7women and 23 men) with advanced heart failure (HF), with mean age 60.134 ±5.6 were included in this study. Twenty seven of these patients fully completed the study while three of them died. They were chosen from outpatient clinic, Eldemerdash hospital, Ain shams university. The purpose, nature and potential risk of the study were explained to all patients. All patients signed a consent form prior to participation in the study.

The inclusion criteria in the studied group were: They were diagnosed with symptomatic (New York heart association class III - IV) systolic left ventricular dysfunction with ≤ 35% left ventricular ejection fraction (LVEF), medical treatment was optimized at least three months prior to study entry, all patients didn't participate in any rehabilitation programs prior to the study. The exclusion criteria were pacemakers, Chronic obstructive pulmonary disease, other disorders and conditions that limited lower limb electrical stimulation (for example, burns, fractures, fixation), pre-existing neuromuscular diseases (for example Myasthenia Gravis) and presence of edema or subcutaneous fat that interfered with the application of neuromuscular stimulation.

Protocol

All patients were evaluated by echocardiography, ergotesting and Minnesota Living with Heart Failure Questionnaire pre and post treatment.

Ergotesting

The patients were asked to avoid strenuous physical activity for 24 h before the tests, and to refrain from eating and smoking for 3 hours before the test. Patients rested for 30 min in a quiet environment.

Arm test: The evaluation of the ergoreflex activity in the arm involves two exercise sessions, performed in random order. (i) A 5 minute session of rhythmic handgrip contractions ,achieved by squeezing the balloon of a sphygmomanometer until 50%of the predetermined maximal capacity (which was obtained by the patient performing two maximal single handgrip contractions) was reached at a frequency of 30 squeezes/min. (ii) The same protocol was followed, immediately from the cessation of exercise, by 3 min of regional circulatory occlusion(RCO), achieved by inflation of an arm tourniquet to30 mmHg above systolic pressure [2].

During test, patients were asked to breathe through a mouthpiece and wearing a nose clip. V_E, VO_2 and Vco_2 were measured by expired gas analysis through a breath-by-breath ergo-spirometer.

The ergoreflex contribution to the ventilatory variables were derived from the absolute difference between 3-minute of post exercise with regional occlusion (PE-RCO) with the 3-minute recovery run without PE-RCO, evaluated as absolute values [2].

Minnesota Living with Heart Failure Questionnaire

Minnesota Living with Heart Failure Questionnaire was completed in the same environment in the hospital out clinic. It was crucial to explain to the patient why it is important to collect his opinions in order to reduce the number of missing data and therefore maximize the quality of the data collected. The instrument was administrated before and after complete protocol application.

Training Procedures

All patients in this study received the following instructions: Patients were instructed to wear loose, short clothing for the lower limbs; they were rested in a sitting position.

Protocol of Low frequency electrical stimulation

The muscles that had been stimulated were the quadriceps and calf muscles of both legs. Self-adhesive surface electrodes 50×90 mm and 50×45mm“for proximal end of Achilles tendon (Fisioline self-adhesive and conductive electrodes) were positioned on the thighs approximately 5cm below the inguinal fold and 3cm above the upper patella border; for the calf muscles the electrodes were positioned approximately 2cm under the knee joint and just over the proximal end of the Achilles tendon.Electrical stimulation was performed 60min/day, 4days/week for 8 consecutive weeks. The stimulator delivered a biphasic current of 15Hz frequency. The current characteristics were set up as follows: "on–off" mode stimulus (20s stimulation, 20s rest), pulse width 200ms, rise and fall time 1s, and maximal stimulation amplitude 65mA [4,5]. The first session of stimulation was started at lower amplitudes (≈30mA) and gradually increased by 10–15mA/day over the following 2–4 days until the final value of 65mA was achieved, which was well tolerated by the patients [4].

Statistical Analysis

Data obtained prior and following management including ventilatoryvariables of the ergoreflex contribution, ejection fraction questionnaire score were statistically analyzed and compared using SPSS program .

RESULTS

General characteristics of the patients:

I- Demographic data:

Descriptive statistics for the demographic data of the 30 patients (23 men and 7 women) included in the study showed a mean values ± standard error (SE) of age (years), weight (kg), height (cm) and BMI (Kg/m2) were 60.13±1.02, 71.03±1.23, 177.40±1.79 and 22.57±0.31 respectively.

II-Studied parameters assessment

Table (1): Descriptive and comparative analysis of the mean values of the studied parameters measured throughout the study

Measured parameter	mean± SE		Paired t-test		change
	Pre	Post	t-value	p-value	
V_E(l/min)	9.40±0.55	-5.67±0.58	6.986	0.000	-37.83%↓
VO_2(ml/min)	10.27±4.79	16.96±3.34	-2.127	0.043	25.46%↑
VCO_2(ml/min)	35.33±6.8	22.30±5.4	5.081	0.000	-36.38%↓
EF%	26.87±0.95	27.93±1.23	-1.578	0.127	2.06%↑
Questionnaire	82.37±1.88	57.26±2.77	12.227	0.000	-29.87%

Data expressed as mean ± SE value. **EF**: Ejection Fraction, **SE:** standard error, **%:** percentage. **p<0.001=highly significant, p<0.005= significant, p>0.005= non-significant **V_E**: minute ventilation, **VO_2:** peak oxygen uptake, **VCO_2**: carbon dioxide production,.

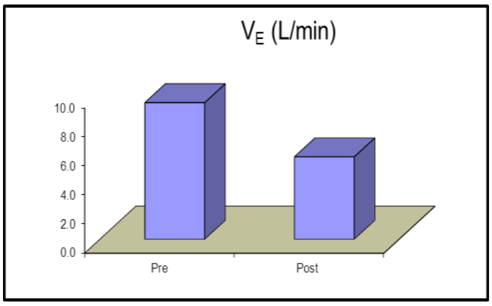

Figure (1): VE measured pre- and post-training

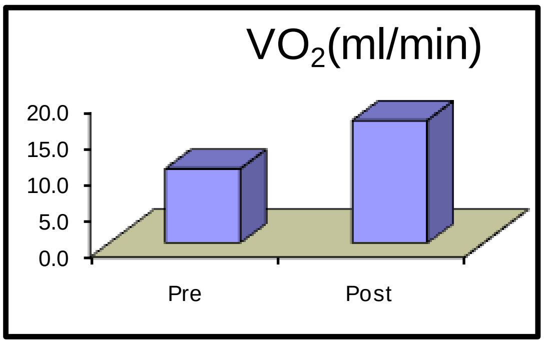

Figure (2): VO_2 measured pre- and post- training

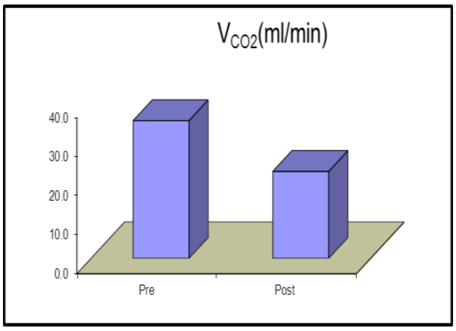

Figure (3): VCO_2 measured pre- and post-raining

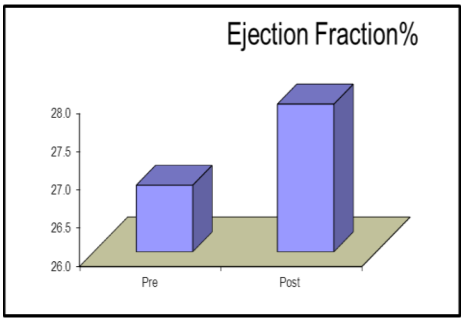

Figure (4): Ejection fraction measured pre-and post-raining

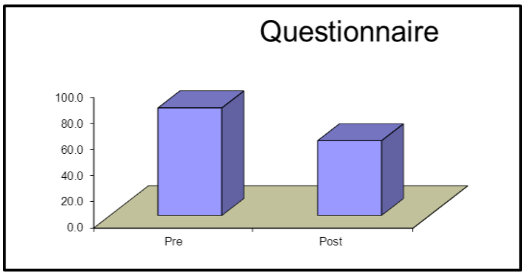

Figure (5): Minnesota Living with Heart Failure Questionnaire measured pre- and post-training

III- Correlation of the studied parameters:

No correlation was found between age of the patients in the studied group and the studied parameters of the study before and after management except for a statistically significant negative correlation between the age of the patients and the post treatment mean value of VO_2 with the r value(-0.484) and p value(0.011) as shown in figure(6).

Negatively statistically significant correlations were observed between the pre-management mean value of the ejection fraction with pre-treatment mean value of V_E with the r value (-0.410) and the p value (0.025) as shown in (7), and between the post-management mean value of the ejection fraction with the post- management mean value of V_E where the value (-0.390) and the p value (0.045) as shown figure (8).

Positive statistically significant correlations were observed between the pre- management mean value of the Minnesota Living with Heart Failure Questionnaire with pre- management mean value of V_E where the value (0.547), and the p value (0.002) as shown in figure (9) and between the post- management mean value of the Minnesota Living with Heart Failure Questionnaire with post- management mean value of V_E where the value (0.585) and the p value (00.001) as shown in figure (10).

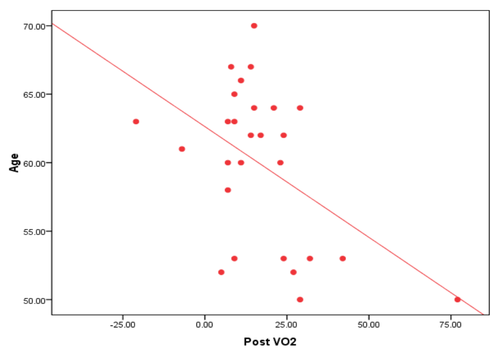

Figure (6): Correlation between the patients' age with VO_2 post-training

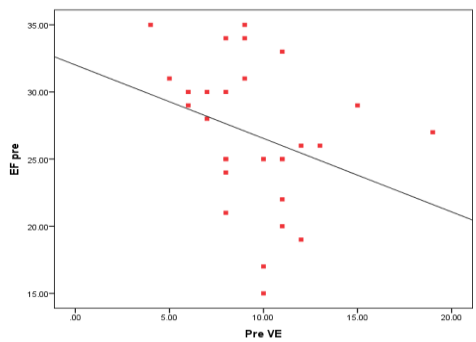

Figure (7): Correlation between ejection fraction pre-management with V_E pre-training

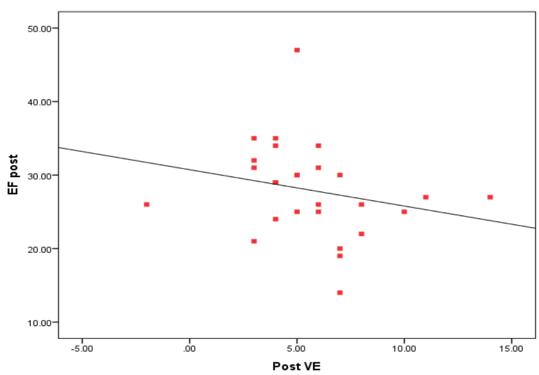

Figure (8): Correlation between ejection fraction post-treatment with VE post-training

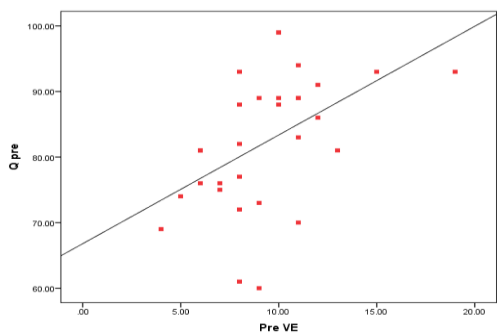

Figure (9): Correlation between Minnesota Living with Heart Failure Questionnaire pre-management with VE pre-training.

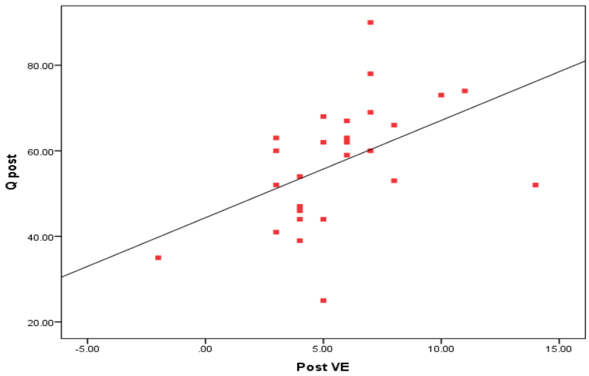

Figure (10): Correlation between Minnesota Living with Heart Failure Questionnaire post-treatment with V_E post-training

DISCUSSION

With breathlessness and fatigue presenting as limiting symptoms of chronic Heart Failure (CHF) the muscle hypothesis has proposed linking such symptoms with the peripheral skeletal muscle changes found abnormal in patients with Chronic Heart Failure (CHF) becoming the source of signals affecting cardiorespiratory control.

The aim of the present study was to test whether or not Low Frequency neuromuscular electrical stimulation is able to safely correct exaggerated ergoreflex activity in thirty patients with advanced heart failure patients with a mean (±SD) age 60.13(±5.60), thus improving their constant sense of fatigue, increasing dyspnea and exercise intolerance and therefore might be used as treatment alternative to exercise in such advanced conditions.

Patients were chosen with BMI ≤ 25with a self-reported unintentional decline in body weight associated with worsened functioning of the patients.

The current study demonstrated that 8 weeks of Low Frequency neuromuscular electrical stimulation (LF-NMES) has caused a significant modulation of ergoreflex contribution with a corresponding improvement in physical, functional, emotional and psychological aspects of patient performance without causing a significant effect on ejection fraction.

The study had also shown that low frequency neuromuscular stimulation is applicable in advanced stages of the disease. This is of special importance, because, for safety reasons, conventional exercise training is advised only for stable less advanced conditions of Heart Failure [6].

Such variables shows significant decrease in V_E and VCO_2 by a change percentage of -37.83%% and -36.38% respectively accompanied by a significant increase in VO_2 by a change percentage of 25.46%. Alteration in ergoreflex variables came hand in hand with significant improvement in quality of life demonstrated by a decrease in Minnesota Living with Heart Failure Questionnaire a change percentage of -29.87% without any significant changes in ejection fraction of the patients with only 2.06% change percentage.

Studies concerning alteration of ergoreflex variables are scarce. The results of the study concerning the ventilatory variables of ergoreflex may be attributed to the expected changes caused by the application of an eight week program of low frequency neuromuscular stimulation such as an alteration of skeletal muscle fiber distribution, a more oxygen uptake kinetics and decreased sympathetic hyperactivity.

The results of the study were also consistent with the results reached by ***Piepoli et al., 1996*** trying to correct ergoreflex hyperactivity and bring it closer to normal by performing six weeks of localized forearm training by patients with symptomatic chronic Heart Failure[7].

Piepoli's study provided clinical support that such localized training did not only increase the exercise capacity of the trained forearm but also partially corrected the exaggerated responses to exercise via a reduction of this reflex contribution. Responses to the abnormal ergoreflex of CHF patients were partially reduced regarding ventilation by -57.6% without causing significant alterations in V_{O2} or V_{CO2} which was expected due to the limited nature of training as the study only included the forearm muscles.

In addition, the changes following LF-NMES in the current study were consistent with the results of the systematic review stated by ***Sillen et al. 2013*** which reported that submitting patients to LF-NMES of the lower extremity muscles has shown marked changes in the skeletal muscle fiber composition[5].

It was stated that the minimum of the programs reviewed of the NMES would show significant changes in peripheral muscle including an increased percentage of type I and type IIa muscle fibers. The changes were combined with significant increase in the activity of the oxidative enzyme Citrate synthase (CS), a marker enzyme for the tricarboxylic acid cycle (Krebs cycle) if applied for a period of 6 weeks of low frequency neuromuscular stimulation. Such increase was associated with an increased resistance to fatigue.

Moreover the changes are consistent with the results reached by ***Labrunée et al. 2013*** studying the effect of acute LF-NMES on sympathetic hyper-activity as assessed by Muscle Sympathetic Nerve Activity (MSNA) through stimulation of quadriceps and calf muscles, using a frequency of 25 Hz [8].

The application of LF-NMES caused a significant decline of the muscle sympathetic activity from 56±3.7 burst/min to 51.6±3.3 burst/min by decreased percentage of -7.85%.

Labrunée was the first to explain the sympatho-inhibitory effect associated with NMES. Labrunée described that the exaggerated sympathetic activity of Heart Failure syndrome shown by an increased ergoreflex significant of both progression and complications of the syndrome. In this study it has been supported that beside the direct effect of the stimulation causing muscular fiber and metabolic changes on chronic application basis, there was a documented acute response; where there was a decline in sympathetic outflow in the lower extremities significant in Heart Failure by the sensory (TENS-like effect) stimulation under the electrode.

The current study also agrees with results reached by***Deley et al.2008*** which suggested that after only 5 weeks of low frequency neuromuscular stimulation, V_{O2} kinetics which was increased by 12.2% which was accompanied by functional improvement assessed by six minute walk test which improved by 13.8% [3].

Non-significant statistical changes were observed in ejection fraction which could be explained by the peripheral nature of low frequency neuromuscular stimulation and also the limited size of the sample.

Such results regarding the non-significant changes of ejection fraction coincided with the results reached by ***Van Buuren et al. 2013*** which stated that limited electrical muscle stimulation for 10 weeks two times a week for 20 minutes on the leg muscles caused a non- significant increase in ejection fraction therefore an extended form of electrical stimulation through a stimulation suit that involved trunk, upper extremity and lower extremity muscles causing a significant statistical increase in ejection fraction by ↑13.3%[9].

No correlation was found between ergoreflexventilatory variables before and after treatment and the studied population age which could be attributed to the nature of skeletal myopathy as a result of aging where there is a decrease in muscle mass primarily caused by type II fiber atrophy and loss in the number of muscle fibers [10], or caused by deconditioning due to increased inactivity associated by an increased expression of MHC1 [11].

Unlike the skeletal changes observed in advanced Heart Failure where there is a shift towards fast isomyosins due to an enhanced activity of mRNA encoding of MCH2b fast fibers [12].

Absence of such correlation between ergoreflex and age of the population supports the benefit gained from applying low frequency neuromuscular stimulation depending on the severity of Heart Failure regardless of the patient's age.

The results of the study also had shown negative correlation between the measured values of V_E and ejection fraction before and after treatment. Such negative relation agrees with the results reached by Piepoli et al., 2006 stating that the clinical deterioration of the syndrome is accompanied with an increased contribution of ergoreflex[2].

A positive correlation existed between the pre- and the post-measured values of V_E and Minnesota Living with Heart Failure Questionnaire, giving evidence of the strong association between an altered ergoreflex and increased disability which is significantly improved after low frequency electrical stimulation, such improvement seen in patients' physical, functional, emotional and psychological status.

CONCLUSION

All the documented improvement in the patients' status after low frequency neuromuscular stimulation were greatly attributed to the patients' acceptance to the nature of stimulating current, thereby causing adherence to the rehabilitation protocol. An informal feedback during the study was captured from the patients sowing tolerance and acceptance to LF-NEMS showing that it could be used as a safe and effective rehabilitation protocol that could partially reverse the abnormal response to exercise in advanced heart failure patients helping in their symptoms and improved activities.

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الملخص العربى

تأثير التنبيه العصبى العضلى على منعكس العمل العضلى فى حالات قصور القلب المتقدمة

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معلوماتأساسية:تعانى حالات قصور القلب المتقدمة من مشاكل ضيق التنفس،الاجهاد الزمن وصعوبة تحمل المجهودقد افترض صلة العصبية بين التغيرات الطرفية وتلك الأعراض المصاحبة .**الهدف:**لتحديد تأثير التحفيز العصبى العضلى منخفض التردد على نشاط منعكس العمل العضلى في حالات قصور القلب المتقدمة .**الأساليب:**أجريت هذة الدراسة على ثلاثين (30) مريض من الرجال والنساء تتراوح اعمارهم بين 50 الى 70تم اختيارهم من العيادات الخارجية لمستشفى الدمرداش، جامعة عين شمس.تم توزيع المرضى على محموعة واحدة لتلقى ثمان أسابيع من تأثير التحفيز العصبى العضلى منخفض التردد وذلك بعد الخضوع لثلاث تقييمات أساسية وهى مخطط صدى القلب، تقييم منعكس العمل العضلى، وتقييم الحالة الوظيفية والعاطفية والنفسيةعن طريق" استبيان مينيسوتا لمرضى قصور القلب". وأظهر المرضى النشاطالمفرط لمنعكس العمل العضلى ربط إيجابيا مع عجزهم المتزايد. وقد أظهرت النتائج بعد الخضوع لثمان أسابيع من التحفيز العصبى العضلى منخفض التردد وجود فروقات ذات دلالة أحصائية وهى انخفاض اثنان من متغيرات منعكس العمل العضلىوهماانخفاض متغير التهوية فى الدقيقة، ومتغيراستهلاك ثانى أوكسيد الكربون نسبة – 37.83%و36.38% على التوالى ، مع ازدياد متغير استهلاك الأوكسيجن بنسبة 25.46%. هذه التغييرات كانت ترتبط بتحسن حالة الوظيفية والعاطفية والنفسية للمرضى مع انخفاض فى" استبيان مينيسوتا لمرضى قصور القلب بنسة–29.87% مع عدم وجود فروق ذات دلالة أحصائية فى الكسر القذفى للقلب بزيادة بنسبة 2.06%.**استنتاج:** التحفيز العصبى العضلى منخفض التردد قد يقلل ازدياد نشاط منعكس العمل العضلى، وبالتالي تحسين الحالة الوظيفية المريض.

الكلمات الدالة:قصور القلب/ التحفيز العصبى العضلى منخفض التردد/العضلات/ منعكس العمل العضلى.